UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,374	06/08/2001	Jeffrey C. Rapp	AVI-007N	2448

26739 7590 11/16/2005

AVIGENICS, INC.
111 RIVERBEND ROAD
ATHENS, GA 30605

EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,374	RAPP, JEFFREY C.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9-29 and 62-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9-29 and 62-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/2/05 has been entered.

Applicants' Amendment, filed 9/2/05, has been entered. Claim 1 has been amended; claims 1-5, 7, 9-29, 62-73 are pending and under current examination.

Claim Rejections - 35 USC § 112

The prior rejection of claims 1-5, 7-29, 62 and 63 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants' amendment to the claims. Particularly, the written description rejection was directed to the lack of description regarding sequences that specifically bind to an antigen. Applicants have now amended the claims such that they read on any heterologous antibody. One of skill in the art could, given the guidance in the specification and that which is readily available in the art, produce a non-specific antibody, as encompassed by the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4, 5, 7, 9, 11, 12, 14-17, 19-29, 62 and 63 are rejected under 35 U.S.C. 102(a) as being anticipated by Ditullio *et al.* [cited in the Office action mailed 10/22/03]. This rejection is maintained for reasons of record advanced on pages 5-8 of the Office action mailed 6/9/05.

Applicants argue that even if the Examiner's characterization of blastodermal cells is correct (that they are considered an embryonic cell), the teachings of Ditullio do not anticipate the claimed invention, because they are drawn to introduction of a nucleic acid into the genome of avian species, and that culturing cells is different than introducing a nucleic acid into blastodermal cells either *in vitro* or *in vivo*. See p. 8 of the Response.

These arguments are not persuasive. Applicants have not provide any guidance as to how the culturing step of the claimed methods differs from that of Ditullio *et al.* Ditullio discloses that the blastoderm cell is removed from the egg and then transfected. This cell is then transferred into the germinal disc of an unfertilized egg to develop into a transgenic chick, or in the testes of a sterile rooster to induce development into spermatogonia and sperm for breeding. See pp. 7-8. Thus, Dituillio contemplate culturing the avian cell *in vitro* and then use the cell in order to produce birds that express a particular antibody. These teachings fulfill the limitations of the claims.

Accordingly, Ditullio anticipate the claimed invention.

Claim 73 is rejected under 35 U.S.C. 102(b) as being anticipated by Heinzel *et al.* [**cited previously**]. This rejection is maintained for reasons of record advanced in the prior Office action, mailed 6/9/05.

Applicants argue that glycosylation patterns produced in avian cells are substantially different than for antibodies produced in mammalian cells. Therefore, Applicants conclude that the structure of the CTLA-4 of the art is unlikely the same as that instantly claimed. Additionally, Applicants argue that avian glycosylation patterns on antibodies can produce antibodies with enhanced characteristics, such as enhanced killing ability. Therefore, the CTLA-4 antibody produced in the present claim may be superior to a similar antibody produced by another method. Applicants cite Zhu *et al.* for support for these arguments. See p. 8 of the Response.

These arguments are not persuasive. Firstly, there is no direct evidence that the CTLA4 antibody taught by the art has different glycosylation patterns or is superior in any way to that taught by the art. Furthermore, Zhu *et al.* specifically state that, "When compared with the same mAb produced from CHO cells, the mAb purified from egg white binds antigen with equal affinity, is internalized into cells expressing the antigen at the same rate, has enhanced ADCC and has an acceptable half-life in mice." See p. 1, 1st column, last sentence. They further state that, "Mab produced in the chicken oviduct and in CHO cells had very similar physical characteristics. Mass spectrometric analysis showed no sequence difference." Although they acknowledge differences in glycosylation patterns, they state that, "Despecite the difference in glycosylation, the chicken- and CHO-produced Mabs had nearly identical binding curves and similar affinities, and were internalized equally by antigen on LNCaP cells." See p. 6, 2nd column, 2nd paragraph. Thus, Zhu supports that antibodies produced in chicken cells function identically and have the same sequence. Therefore, it is maintained that Heinzel anticipate the claimed invention.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See

In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Claim 73 is rejected under 35 U.S.C. 102(e) as being anticipated by Carreno *et al.* **[Pub. No. US 2002/0039581 A1**, published April 4, 2002, filed Jan. 26, 2001].

Applicants' arguments to this rejection are the same as those addressed above. It is maintained that Carreno anticipate the claimed invention, because they teach the production of human CTLA4 antibodies.

The claim is a product-by-process claim (see above). Carreno teach the production of CTLA4 antibodies, and specifically those that react to human CTLA4. See p. 1, paragraphs 6-9. Accordingly, they anticipate the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of claims 1, 3, 10, 13 under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* when taken with Michael *et al.* is maintained for reasons of record.

Applicants submit that one reason the rejected claims are not made obvious by the cited references, is because all the elements required for a finding of obviousness are not present in the cited references, for example, the invention of Ditullio is drawn to protein production in transgenic avian, and the present invention is drawn to the production of antibodies in cell culture. See pp. 8-9 of the Response.

These arguments are not persuasive. Ditullio discloses that the blastoderm cell is removed from the egg and then transfected. This cell is then transferred into the germinal disc of an unfertilized egg to develop into a transgenic chick, or in the testes of a sterile rooster to induce development into spermatogonia and sperm for breeding. See pp. 7-8. Thus, Dituillio contemplate culturing the avian cell *in vitro* and then use the cell in order to produce birds that express a particular antibody. These teachings fulfill the limitations of the claims.

Ditullio differ from the claimed invention in that they do not teach or suggest the expression vector further encodes a second immunoglobulin polypeptide and an IRES, that the vector is a viral vector, and that the promoter is the cytomegaloviral promoter. However, prior to the claimed invention, Michael teach methods of producing monoclonal antibodies in an avian system, and in particular, chickens. They teach that the CMV immediate early gene promoter is a promoter that can be used to obtain high-level of expression of a coding sequence of interest, and that by employing such a well-known promoter, the level and pattern of expression can be optimized (see col. 16, lines 47-63). Michael further teach that the use of IRES elements can create multigene, or polycistronic messages. They teach that IRES elements can be linked to heterologous open reading frames, and that by virtue of the IRES element, multiple genes can be efficiently expressed by a single promoter

or enhancer to transcribe a single message [col. 19, lines 5-21]. Michael teach that genetic constructs can be introduced into cells by both viral and non-viral transduction. Viral methods include adenoviral, and adeno-associated viral vectors [col. 19, lines 30-45].

Accordingly, in view of the combined teachings of Michael and Ditullio, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the methods of generating antibodies from avian cells, as taught by Ditullio, by use of the cytomegaloviral promoter, an IRES element, or by use of a viral vector, as taught by Michael, with a reasonable expectation of success. One of ordinary skill would have been sufficiently motivated to make such a modification, as supported by Michael, that the cytomegaloviral promoter is a well-known and well-characterized promoter that would allow for optimal levels and patterns of gene expression, that utilizing an IRES element would facilitate expression of multiple genes, and that viral transduction is an efficient way to deliver a construct to a cell.

Claims 64-73 rejected under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* when taken with Ling *et al.* [**Genomics**, 60:341-355 (1999)] and Najafian *et al.* [Exp. Opin. Invest. Drugs. 9(9): 2147-2157 (2000)].

Applicants' argue, as above, that Ditullio do not teach the claimed invention, and thus, the combination of references fails to arrive at the claimed invention. See p. 9 of the Response. These arguments have been addressed above.

Ditullio teach methods of generating transgenic avian. In particular, they teach the introduction of a nucleic acid molecule into the genome of an avian aspecies by contacting *in vivo* a blastodermal cell of a fertilized hard shelled egg [see p. 1-2]. The avian species can be, for example, a chicken [see p. 2, lines 9-12]. DiTullio teach that the nucleic acid can contain a sequence encoding an antibody or fragment thereof, for example, a monoclonal antibody, or a chimeric molecule [*e.g.,*

containing antibody portions of both murine and human origin] [see p. 2, lines 22-28]. Ditullio discuss the transcriptional regulatory elements that are contained in the nucleic acid construct, such as initiation signals, enhancers, promoters, which induce or control the transcription of protein coding sequences to which they are operably linked [see p. 3, lines 1-5]. For example, the promoter may be constitutive or inducible, and may be tissue-specific, inducible by external signals or within an intron [see p. 3, lines 12-15]. Ditullio teach that the chicken lysozyme or ovalbumin promoter may be used with the described transgene construct [see p. 3, lines 15-17]. In particular, the invention includes a transgene expression cassette in which the heavy and light chain coding regions of an antibody are ligated together, each under the direction of its own promoter operably linked to a matrix attachment region [see p. 3, lines 24-26]. Ditullio that the avian cell can be targeted either *in vitro* or *in vivo* [see pp. 7-10]. In particular, the cells of the blastoderm can be accessed by cutting or drilling a small hole in the eggshell and directly infusing the DNA into the blastoderm [see p. 7].

Ditullio do not specifically teach producing an antibody specific for CTLA4. However, prior to the time the claimed invention was made, Ling teach the sequence of human CTLA4, including its alignment with the mouse CTLA4 sequence. See Figure 3. Ling teach that CTLA4 has been correlated with specific diseases (see p. 341, 2nd column). Najarfian provide the requisite motivation for the production of CTLA4 antibodies, as instantly contemplated. They teach that CTLA-4 is only expressed on activated T-cells, and that CTLA-4 negative signaling pathways maybe required for the induction of acquired tolerance. See p. 2148, 2nd column, Introduction.

Accordingly, in view of the combined teachings, it would have been obvious for the skilled artisan to modify the technique of producing antibodies in avian species, as taught by Ditullio, utilizing a construct encoding CTLA-4, with a reasonable expectation of success. One of ordinary skill in the art would have been

motivated to make such a modification, as the art recognizes the importance of suppressing CTLA-4 to generate acquired tolerance, for example.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-5, 7, 9-29, 62 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* (cited above) when taken with Mohammed *et al.* [**Immunotechnology**, 1998, 4:115-125, cited in the Office action mailed 1/30/03].

Ditullio teach the introduction of a nucleic acid molecule into the genome of an avian species by contacting *in vivo* a blastodermal cell of a fertilized hard shelled egg [see p. 1-2]. The avian species can be, for example, a chicken [see p. 2, lines 9-12]. DiTullio teach that the nucleic acid can contain a sequence encoding an antibody or fragment thereof, for example, a monoclonal antibody, or a chimeric molecule [*e.g.,* containing antibody portions of both murine and human origin] [see p. 2, lines 22-28]. Ditullio discuss the transcriptional regulatory elements that are contained in the nucleic acid construct, such as initiation signals, enhancers, promoters, which induce or control the transcription of protein coding sequences to which they are operably linked [see p. 3, lines 1-5]. For example, the promoter may be constitutive or inducible, and may be tissue-specific, inducible by external signals or within an intron [see p. 3, lines 12-15]. Ditullio teach that the chicken lysozyme or ovalbumin promoter may be used with the described transgene construct [see p. 3, lines 15-17]. In particular, the invention includes a transgene expression cassette in which the heavy and light chain coding regions of an antibody are ligated together, each under the direction of its own promoter operably linked to a matrix attachment region [see p. 3, lines 24-26]. Ditullio that the avian cell can be targeted either *in vitro* or *in vivo* [see pp. 7-10].

Although Ditullio teach that the cell can be targeted *in vitro* or *in vivo*, they do not contemplate that the cell can produce an antibody outside of the context of

producing a transgenic avian that produces the antibody. However, prior to the time the claimed invention was made, Mohammed teach expression of recombinant human antibodies in stably transfected DT40 cell lines. In particular, Mohammed teach that two types of vectors were developed, one with the heavy chain of the immunoglobulin which results in the expression of a murine anti-dansyl variable region joined to the appropriate human heavy chain constant region. The other vector encodes the light chain which results in the expression of a corresponding murine anti-dansyl variable region joined to a human kappa light chain constant region. [See pp. 116-117, bridging ¶]. Mohammed teach that these two vectors were co-transfected with each of the vectors into a chicken B lymphoblastoid cell line, DT40 [see p. 117, section 2.2.]. The transfected cells were maintained in culture media for two days, wherein surviving colonies were screened by ELISA to verify expression of the chimeric antibodies.

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art, to use the cells and methods taught by Ditullio, and modify these methods to express a vector encoding an antibody by culturing a cell and isolating the antibodies from a cell, such as those contemplated by Ditullio, with a reasonable expectation of success. One of ordinary skill would have been sufficiently motivated to make such a modification, because cell lines expressing recombinant human antibodies could be used to inject into laying hens, in order to produce transgenic hens which express the antibody in their egg yolk. This expression would increase the yield of antibodies, and allow for simple purification of the protein. See also, Mohammed, Abstract.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tnt

Thaian N. Ton

Patent Examiner

Group 1632

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER